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CARDIOTROPHIN-1 AS AN INDEPENDENT FACTOR OF EARLY DEVELOPMENT OF ATHEROSCLEROTIC CHANGES IN COMORBID PATIENTS

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The work is devoted to the study of cardiotrophin-1 as a crucial biomarker for the early development of atherosclerotic changes in patients with comorbid conditions, such as arterial hypertension, type 2 diabetes mellitus, and obesity. Considering the high prevalence of these conditions, the early detection of factors contributing to cardiovascular complications is of paramount importance. The study included 211 patients aged 49 to 65 years, divided into four groups based on the presence of arterial hypertension, type 2 diabetes mellitus, and obesity. The results show a significant increase in the level of cardiotrophin-1in patients with comorbid pathology compared to healthy individuals. The study found that cardiotrophin-1is not only an indicator of early cardiovascular complications but also a prognostic factor for the development of atherosclerosis. A positive correlation between cardiotrophin-1 levels and the atherogenic index was also established in all patient groups.

Key words: cardiotrophin-1, arterial hypertension, type 2 diabetes mellitus, obesity, atherosclerosis, comorbid conditions, biomarkers.

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КАРДІОТРОФІН-1 – ЯК НЕЗАЛЕЖНИЙ ФАКТОР РАННЬОГО РОЗВИТКУ АТЕРОСКЛЕРОТИЧНИХ ЗМІН У КОМОРБІДНИХ ХВОРИХ

Робота присвячена дослідженню ролі кардіотрофіну-1 як важливого біомаркера раннього розвитку атеросклеротичних змін у пацієнтів із коморбідними станами, такими як артеріальна гіпертензія, цукровий діабет 2 типу та ожиріння. З огляду на високу поширеність цих станів, важливим завданням є своєчасне виявлення факторів, що сприяють розвитку серцево-судинних ускладнень. У дослідженні взяли участь 211 пацієнтів віком від 49 до 65 років, яких розподілили на чотири групи залежно від наявності артеріальної гіпертензії, цукрового діабету 2 типу та ожиріння. Отримані результати свідчать про значне підвищення рівня кардіотрофіну-1у пацієнтів із коморбідною патологією порівняно зі здоровими особами. Дослідження виявило, що кардіотрофін-1є не тільки індикатором раннього розвитку серцево-судинних ускладнень, але й має прогностичне значення для розвитку атеросклерозу. Також встановлено позитивну кореляцію між рівнем кардіотрофіну-1 та атерогенним індексом у всіх групах пацієнтів.

Ключові слова: кардіотрофін-1, артеріальна гіпертензія, цукровий діабет 2 типу, ожиріння, атеросклероз, коморбідні стани, біомаркери.

The work is a fragment of the research project "To determine the features of immuno-cytokine imbalance in comorbid patients with hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

The prevalence of comorbidities is increasing worldwide today, therefore, the comorbid patient is gaining much attention from clinicians. The most widespread comorbidities include the combination of arterial hypertension (AH), type 2 diabetes mellitus (T2DM), and obesity (OB), thus determining a high cardiovascular risk and calling for a search for the most recent diagnostic capabilities to detect early development of complications in such patients [1, 2].

Cardiotrophin-1 (CTF-1) is a highly informative marker for the early development of cardiovascular complications in patients with combined AH pathology with T2DM and OB. Therefore, the determination of its properties is actively discussed worldwide [3, 4, 5].

Key properties of this biomarker include its contribution to the regulation of cardiac remodeling, promitotic and proliferative properties, ability to induce cardiomyocyte hypertrophy, etc. [6, 7, 8, 10].

The findings of studies showing a close relationship between the concentration of CTF-1 and the severity of left ventricular myocardial hypertrophy in patients with AH and T2DM are of great importance [9].

The purpose of the study was to identify the contribution ofcardiotrophin-1 in patients with arterial hypertension, type 2 diabetes mellitus, and obesity in the development of early atherosclerotic changes.

Materials and methods. This study was performed according to the ethical and moral requirements of the Ukrainian Association for Bioethics and the norms of GCP (1992), GLP (2002), the principles of the Declaration of Helsinki on Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and approved by the Ethics and Bioethics Committee of Kharkiv National Medical University.

211 patients aged 49 to 65 years, who were treated at the clinic of the Government Institution "L.T. Malaya Therapy National Institute" of the National Academy of Medical Sciences of Ukraine, were included in the study, which was conducted during 2021–2023. They were divided into groups depending on the pathology: patients with AH – 49 people, group I; patients with AH and I grade OB – 54 people, group 2; patients with AH and T2DM – group 3; patients with AH, T2DM, and I grade OB – 51 people, group 4; and a control group of 20 people. The study groups of patients were age- and gender-matched.

All the patients' body weight and height were measured, and BMI = body weight/height (m^2) was calculated. The body mass index (BMI) was defined to detect obesity (BMI>30 kg/m^2), according to WHO criteria. AH, its degree and stage were confirmed according to current European guidelines, while diabetes was diagnosed according to WHO criteria.

All patients have signed an informed consent to take part in the study.

These are the exclusion criteria for the study: Type 1 diabetes mellitus, congenital heart and urinary tract defects, artificial pacemakers, artificial heart valves, stage II B and III heart failure, acute myocardial infarction, infectious and severe inflammatory processes, and hematological diseases.

CTF-1, catestatin, leptin, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), N-terminal brain natriuretic peptide (NT-proBNP), 25-OH total vitamin D (Vitamin D3), and serum insulin levels were determined by enzyme-linked immunosorbent assay with a Labline-90 analyzer (Austria) using commercial test systems manufactured by Fine Test (ELISA, China), BT LAB (ELISA, China), DBC (ELISA, China), Elabscience (ELISA, Canada), Monobind Inc. (ELISA, USA), according to the instructions included in the kits.

Biochemical studies (serum creatinine, urea, and lipid spectrum) were performed with a Labline-90 analyzer (Austria). The serum urea level was measured by the kinetic, enzyme-linked assay with urease and glutamate dehydrogenase using Liquick Cor-UREA 30 kits (Cormay, Poland) according to the manufacturer's instructions. The serum creatinine level was measured by the modified Jaffe's method without deproteinization using Liquick Cor-CREATININ 30 reagent kits (Poland) according to the manufacturer's instructions. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined by the enzyme-linked assay using Cholesterol liquicolor, HDL-Cholesterol, and Triglycerides liquicolor reagent kits (Human, Germany) according to the manufacturer's instructions.The content of very low-density lipoprotein (VLDL-C) was calculated using the formula of TG/2.22; the content of low-density lipoprotein (LDL-C) was calculated using the formula of W. T. Friedewald, 2004:

$$LDL\text{-}C=TC-(HDL\text{-}C+TG/2.22),\ mmol/l.$$

The obtained data were statistically analyzed using the software packages Statistica v. 13.3, SPSS v. 26.0, MedCalc v. 19.2.0, and EZR v. 1.41. To describe the quantitative data, the sample standard deviation (σ) and median (Me) were calculated, and the upper and lower quartiles [Q1; Q3] were used for interval estimation since the sample was subject to the law of normal distribution.The Mann-Whitney U test was used to compare the findings of the studies in two independent samples, and the Wilcoxon test was used to compare the variables of the dependent samples.The relationship between quantitative variables was assessed using Spearman's rank correlation coefficient (rs). To assess the correlation level, the Cheddock scale was used. Differences were considered statistically significant at$\rho<\alpha$, whereα is the first-order error ($\alpha = 0.05$). To distribute qualitative indicators, the 95 % confidence interval (CI) was calculated. The correlation analysis was performed with the nonparametric Spearman correlation coefficient (ρ), and the relationship strength was interpreted according to the following gradations: $|\rho|<0.3$ –weak correlation; $0.3\leq|\rho|<0.7$–medium correlation; $|\rho|\geq0.7$–strong correlation. Two correlations were compared using the MedCalc v. 19.2.0 software package. Univariate and stepwise multivariate logistic regression analysis was performed to determine the most closely associated factors. The correlation between the factor attributes in the logistic regression models was assessed using the odds ratio, for which the 95 % CI was determined.

Results of the study and their discussion. The findings of the above test demonstrate that the CTF-1 level in the examined groups of patients differs significantly both compared to the control group and to each other. For instance, CTF-1 level in the group of patients with AH was 689.9±72.2, which was significantly higher ($p\leq0.001$) compared to the control group (366.7±45.57) and to the groups of patients with comorbidities: AH+OB is 1024.3±81.2, AH+T2DM is 1113.4±75, AH+OB+T2DM is 1290.1±38.9 ($p\leq0.001$).

While conducting this study, we assessed the dependence of the studied parameters on the CTF-1 level (Table 1).

Table 1

Dependence of laboratory indicators on CTF-1 level

Marker, measurement unit	Cardiotrophin-1 level below 1148.75	Cardiotrophin-1 level over 1148.75	p
Age	53.80±3.86 [49.0; 62.0]	51.42±2.73 [45.00; 60.50]	0.033
BMI, kg/m^2	30.92±4.40 [29.42; 36.22]	32.30±1.11 [28.11; 34.22]	0.031
SBP, mmHg	144.47±10.55 [139.8; 155.7]	147.55±4.11 [140.0; 156.0]	0.174
DBP, mmHg	90.05±7.84 [83.0; 96.7]	88.75±2.11 [80.0; 95.5]	0.441
Creatinine, μmol/l	93.80±8.86 [83.95; 101.40]	95.26±2.11 [85.70; 103.40]	0.326
Urea, mmol/l	5.94±0.69 [4.60; 6.76]	5.89±0.33 [4.43; 7.21]	0.223
TC, mmol/l	5.47±0.81 [4.70; 6.42]	5.88±0.22 [5.05; 6.60]	0.167
HDL-C, mmol/l	1.26±0.16 [0.95; 1.50]	1.37±0.11 [1.10; 1.55]	0.077
TG, mmol/l	1.91±0.23 [1.30; 2.25]	1.98±0.23 [1.45; 2.30]	0.465
VLDL-C, mmol/l	0.86±0.15 [0.60; 1.00]	0.89±0.11 [0.65; 1.00]	0.433
LDL-C, mmol/l	3.35±0.29 [2.50; 4.10]	3.62±0.24 [2.55; 4.30]	0.317
AI	3.53 ±0.33 [2.40; 4.30]	3.52±0.21 [2.60; 4.25]	0.256
CTF-1, pg/ml	853.97±133.6 [658.20; 1054.53]	1241.26±30.54 [1181.51; 1313.55]	0.001
Catestatin, ng/ml	2.90±0.22 [1.84; 6.75]	2.80±0.22 [2.09; 2.76]	0.227
Cystatin C, mg/l	138.44±15.64 [101.11; 162.67]	129.43±4.43 [81.41; 174.39]	0.295
Leptin, ng/ml	26.09±2.02 [14.06; 34.14]	28.14±1.22 [19.27; 33,38]	0.227
Neutrophil gelatinase-associated lipocalin (NGAL), ng/ml	19.50±1.33 [15.32; 23.64]	19.26±1.11 [15.01; 23.15]	0.147
N-terminal prohormone of brain natriuretic peptide (NT-proBNP), pg/mL	471.33±26.11 [386.68; 551.61]	518.47±45.62 [341.70; 652.60]	0.141
Insulin, pmol/l	15.73±1.79 [8.54; 23.06]	15.14±2.11 [10.36; 21.46]	0.116
β2-MG, mg/ml	3.06±0.55 [2.49; 3.94]	3.20±0.28 [2.56; 3.96]	0.106
Vitamin D3, ng/ml	40.45±2.44 [32.76; 48.76]	41.01±1.77 [28.88; 48.77]	0.221
Glycated hemoglobin (HbA1c), %	5.70±0.23 [4.77; 8.20]	6.76±0.25 [6.21; 7.14]	0.001

According to the univariate regression analysis, the β-coefficients of all included indicators were statistically significant, so they were added to the multivariate analysis.

We present the β-coefficient, standard error (SE), Wald statistic (W), number of degrees of freedom (df), p-value (significance level), and odds ratio (OR) with 95 % confidence interval (CI) for each indicator (Table 2).

When analyzing the findings, it was found that the older age of the patient was associated with an increase in the CTF-1 level, which is likely to be a consequence of changes in the cardiovascular system. This confirms the existence of a possible connection between changes in CTF-1 levels and population aging. The most prominent difference was found between the CTF-1 level and HbA1c, which demonstrates a potential relationship between CTF-1 and the risk of developing diabetic complications, namely diabetic cardiomyopathy [12].

The results of the univariate analysis revealed that age, gender, BMI, CTF-1 levels, catestatin, cystatin C, leptin, NGAL, NT-proBNP, insulin, and HbA1c levels were significant ($p<0.05$), indicating their potential impact on the development of complications.

Table 2

Factors influencing the CTF-1 level

Indicator	Univariate analysis						Multivariate analysis					
	β	SD	W	df	p	Odds ratio (95 % CI)	β	SD	W	df	p	Odds ratio (95 % CI)
Age	0.113	0.01	7.93	1	0.02	1.19 (1.12–1.29)	-	-	-	-	-	-
Gender	1.078	0.36	10.34	1	0.03	2.69 (1.47–4.91)	-	-	-	-	-	-
IMT	1.201	0.31	18.08	1	0.01	2.99 (1.80–4.96)	-	-	-	-	-	-
CTF-1	1.367	0.31	21.93	1	0.01	3.43 (2.03–5.78)	-	-	-	-	-	-
Catestatin	2.269	0.62	16.07	1	0.02	7.29 (2.65–20.06)	1.39	0.61	5.21	1	0.02	4.02 (1.21–13.2)
Cystatin C	1.178	0.31	17.03	1	0.03	2.93 (1.76–4.89)	0.92	0.31	5.21	1	0.02	2.27 (1.127–4.6)
Leptin	0.311	0.07	21.96	1	0.01	1.41 (1.26–1.60)	-	-	-	-	-	-
NGAL	1.321	0.62	5.46	1	0.03	3.31 (1.19–9.14)	-	-	-	-	-	-
NT-proBNP	2.818	0.46	44.71	1	0.03	11.56 (5.42–24.47)	1.55	0.33	12.22	1	0.02	4.70 (1.55–9.55)
Insulin	2.135	0.42	30.25	1	0.04	6.51 (3.24–13.04)	1.21	0.43	5.44	1	0.01	2.11 (1.11–6.33)
Glycated hemoglobin (HbA1c)	0.637	0.32	4.68	1	0.04	1.87 (1.11–3.16)	-	-	-	-	-	-

Multivariate analysis revealed independent predictors of the risk of cardiovascular complications. It was found that one of the key independent factors is catestatin, followed by cystatin C, and NT-proBNP is an essential indicator in the prognosis of cardiovascular complications.

The present study proved that the evaluation of such parameters as CTF-1, catestatin, cystatin C, NT-proBNP, and insulin can be considered as independent predictors of cardiovascular complications in comorbid patients with AH, T2DM, and OB. These findings show the correlation of CTF-1 with other indicators, stressing the need for further study of catestatin, cystatin C, NT-proBNP, and insulin to develop effective strategies for early diagnosis and prevention of complications in high-risk patients, which is consistent with the work of other researchers [13, 14, 15].

Our findings suggest that CTF-1 is not only a biomarker for the early development of cardiovascular complications, but also a prognostic factor for the early development of atherosclerotic changes in comorbid patients. These findings imply the need for additional examinations to identify high-risk individuals, which is consistent with the work of other researchers concerning the requirements for additional examination of patients with a high cardiac risk of disease progression, complications, and prognosis [11].

Conclusions

1. It has been found that the serum concentration of CTF-1 in patients with arterial hypertension is significantly higher compared to healthy individuals and is increased depending on the presence of comorbidities.

2. The positive correlation of cardiotrophin-1 with the atherogenicity coefficient in all examined groups of patients suggests its independent influence on the early development of atherosclerotic changes in patients with arterial hypertension, type 2 diabetes mellitus, and obesity.

3. It has been proven that cardiotrophin-1 has a significant effect on the development of cardiovascular complications in comorbid patients and its association with catestatin, cystatin C, N-terminal prohormone of brain natriuretic peptide, and insulin, which demonstrates the complexity of the pathophysiological processes underlying comorbid pathology.

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